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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/681,627	10/08/2003	Carl H. June	WYS-01402	7408

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EXAMINER	
LEAVITT, MARIA GOMEZ	
ART UNIT	**PAPER NUMBER**
1633	

SHORTENED STATUTORY PERIOD OF RESPONSE	MAIL DATE	DELIVERY MODE
3 MONTHS	01/18/2007	PAPER

Please find below and/or attached an Office communication concerning this application or proceeding.

If NO period for reply is specified above, the maximum statutory period will apply and will expire 6 MONTHS from the mailing date of this communication.

Office Action Summary	Application No.	Applicant(s)	
	10/681,627	JUNE, CARL H.	
	Examiner	Art Unit	
	Maria Leavitt	1633	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *30 October 2006*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-38* is/are pending in the application.

4a) Of the above claim(s) *10-14,18,21 and 23-38* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-9,15-17,19,20 and 22* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☒ The drawing(s) filed on *08 October 2003* is/are: a)☐ accepted or b)☒ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date *03-04-04, 09-21-06*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

Applicant election **with traverse** of Group I, drawn to claims 1-6, 8-9, and 15-22 in response to the Requirements for Election/ Restriction filed on 06-27-2006 is acknowledged. Election of the following species, with traverse, autoantigen as the antigen, is acknowledged. Claims 18 and 21 are withdrawn from consideration as being directed to a non-elected species. See 37 CFR 1.142(b) and MPEP § 821.03.

The instant invention claims to be a divisional of US Application No. 08/245,282, now Patent 6,632,789, Date of publication Oct. 14, 2003. However, the examiner considers the instant application to be a continuation of Application No. 08/245,282, now Patent 6,632,789, as the instant claims do not read on specific groups of the initial restriction made for Application No. 08/245,282.

Response to arguments

On page 3 of Applicant's Remarks, Applicant argues that Groups I-III belong to the same class and subclass and as such a search encompassing Groups I-III would not place a serious burden on the Examiner. Such is not persuasive.

As stated in the Office Action mailed on 06-27-2006, though inventions of Groups I-III belong to the same the same class and subclass and share in their methods the step of contacting a T cell with an inhibitor of phosphtidylinositiol 3-kinase, the methods are patentably distinct and they do not overlap in scope or are not obvious variants of each other as each method comprises contacting the cell with a second agent, e.g., an inhibitor of a protein tyrosine kinase (Group I), or a tyrosine phosphatase (Group II), or a molecule that binds to and activates CD45

(Group III), that are materially different in structural, chemical, physical, and functional properties and as such the search for each of the second agents is not coextensive. Thus, it would place an undue burden on the examiner to search and examine Groups I-III together.

The requirement is still deemed proper and is therefore made FINAL.

Therefore claims 1-6, 7-9, 15-17,19-20 and 22 are pending for examination to which the following grounds of rejection are applicable.

Claim Rejections - 35 USC § 102

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

A person shall be entitled to a patent unless –

> (e) the invention was described in (1) an application for patent, published under section 122(b), by another filed in the United States before the invention by the applicant for patent or (2) a patent granted on an application for patent by another filed in the United States before the invention by the applicant for patent, except that an international application filed under the treaty defined in section 351(a) shall have the effects for purposes of this subsection of an application filed in the United States only if the international application designated the United States and was published under Article 21(2) of such treaty in the English language.

Claims 1-6 are rejected under 35 U.S.C. 102(e) as being anticipated by Bonjouklian et al., U.S. Patent No. 5,504,103, Date of Publication, April 2 1996 (hereafter referred to as Bonjouklian et al.)

The present invention is drawn to methods of inhibition of T cell response by inhibitors of phosphatidylinositol 3-kinase (P13K) inhibiting production of D-3 phosphoinositides in the T cell upon CD28 ligation. Claim 3 further limits the invention to an inhibitor of

phosphatidylinositol-3-kinase, e.g., wortmannin. It is noted that the only active method steps in the instant claims is the step of contacting a T cell with an agent, such as wortmannin. Moreover, the present inhibition teaches that inhibition of PI3K activity in a T cell inhibits T cell responses, such as cytokine production and cellular proliferation.

Bonjouklian et al., teach methods of treating phosphatidylnositos-3-kinase dependent conditions in a mammal comprising contacting the cell with wortmannin or wortmannin analog (col. 14-16, claims 1-20). While Bonjouklian et al., teach the exact same method step as the instant claims (i.e. contacting cells with wortmannin), Bonjouklian et al., do not expressly teach contacting T cells or specifically T cells which express a CD28 receptor with wortmannin. Bonjouklian et al., also do not expressly teach the modulation of T cell proliferation or modulation of lymphokine production. However, it is inherent in the methods taught by Bonjouklian et al., that the administration of wortmannin or wortmannin analogs to a mammal results in the inhibition of phosphatidylinositol 3-kinase in any and all cells in mammals which express phosphatidylinositol 3-kinase. T cells are abundantly present in mammals and inherently express phosphatidylinositol 3-kinase. This finding is supported by the applicant disclosure in Figures 3, 4, 7a and 7b that contacting CD28 positive T cells with wortmannin results in inhibition of phosphatidylinositol 3-kinase. Thus, as it is clear that if T cells express phosphatidylinositol 3-kinase, it is inherently in the method of inhibiting phosphatidylinositol 3-kinase in the cells in a mammal *in vivo* as taught by Bonjouklian et al., that phosphatidylinositol 3-kinase is inhibited in T cells present in that mammal. Furthermore, the inhibition of phosphatidylinositol 3-kinase in T cells necessarily and inherently results in a change in cellular

activities dependant on phosphatidylinositol 3-kinase, such as proliferation and lymphokine production.

Furthermore, case law clearly teaches that "merely discovering and claiming a new benefit of an old process cannot render the process again patentable" , see *In re Woodruff* 919 F 2.d 1575, 1577-78, 16USPQ2d 194, 1936-37 (Fed. Cir. 1990); *In re Swinehart* 439 F 2.d 210, 213, 169 USPQ 226, 229 (CCPA 1971); and *Ex parte Novitski* 26 USPQ2d 1389, 1391, (Bd. Pat. App. & Int. 1993). The MPEP also states, "when the claim recites using an old composition or structure and the "use" is directed to a result or property of that composition or structure, then the claim is anticipated. *In re May*, 574 F.2d 1082,1090, 197 USPQ 601, 607 (CCPA 1978). MPEP 2112.02. In the instant case discussed above, Bonjouklian et al., clearly teaches that wortmannin inhibits phosphatidylinositol 3-kinase and further teach contacting cells both *in vitro* and *in vivo* with wortmannin in order to inhibit phosphatidylinositol 3-kinase. Thus wortmannin is an old composition with a known ability to inhibit phosphatidylinositol 3-kinase and the applicant's use of wortmannin for inhibiting phosphatidylinositol 3-kinase in T cells represents a "use" of wortmannin that is based in an inherent property of wortmannin. As such Bonjouklian et al., anticipates the instant invention.

Claim Rejections - 35 USC § 112 - enablement

The following is a quotation of the first paragraph of 35 U.S.C. 112:

The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 15-17,19-20 and 22 are rejected under 35 U.S.C. 112, first paragraph, because the specification is enabling only for claims limited to:

An *in vitro* method for inhibiting T cell activation as assessed by production of IL-2 comprising stimulating a T cell through the TCR/CD3 complex and CD28 and further contacting said T cell with Wortmannin thereby inhibiting the activity of phosphatidylinositol 3-kinase within the T cell.

The specification does not reasonably provide enablement for claims directed to a method of inducing unresponsiveness to an antigen in a T cell and further administering the T cell to a subject suffering from an autoimmune disease.

The specification does not enable any person skilled in the art to which it pertains or with which it is most nearly connected, to use the invention commensurate in scope with this claim. Factors to be considered in determining whether a disclosure meets the enablement requirement of 35 USC 112, first paragraph, have been described by the court in *In re Wands*, 8 USPQ2d 1400 (CA FC 1988). *Wands* states at page 1404,

> "Factors to be considered in determining whether a disclosure would require undue experimentation have been summarized by the board in Ex parte Forman. They include (1) the quantity of experimentation necessary, (2) the amount of direction or guidance presented, (3) the presence or absence of working examples, (4) the nature of the invention, (5) the state of the prior art, (6) the relative skill of those in the art, (7) the predictability or unpredictability of the art, and (8) the breadth of the claims."

The claims, when given the broadest possible interpretation, encompass a method for inducing unresponsiveness to an antigen in a T cell and further administering said T cell to a subject suffering from an autoimmune disorder with the contemplated treatment and/or

prevention of said disorder. The subject could be reasonably construed as a human subject suffering from any type of autoimmune disease (e.g., rheumatoid arthritis, Crohn's disease, psoriasis, asthma, myasthenia gravis, chronic inflammatory demyelinating polyneuropathy). The specification provides insufficient data to enable claims directed to the method as broadly claimed. Thereby, specific issues including treatment of a complex autoimmedisorder associated with abnormal immune responses have to be examined and considered for patentability regarding the broadly claimed methods.

The instant specification discloses on pages 17, Example 4, the effects of Wortmannin, which inhibits the activity of protein tyrosine kinases, in Jurkat cells that were stimulated with CD28 antibody. Moreover in Example 5, page 18, the as-filed specification teaches that Wortmannin inhibits stimulation of T cells as measured by IL-2 production induced by costimulation with B71 or B7-2 in conjunction with CD3 stimulation. The results demonstrate that T cell activation can be inhibited by treatment of the T cells with Wortmannin, which inhibits the activity of protein tyrosine kinases. Further, Applicant contemplates on pp. 9-10, (lines 37 and 1-10) a wide number of diseases where it is desirable to downmodulate an immune response that can be treated by inducing T cell unresponsiveness such as arthritis, juvenile rheumatoid arthritis, psoriatic arthritis, allergies, contact dermatitis, psoriasis. However, the as-filed application is silent about any factual data disclosing a method of treating autoimmune diseases in a subject. The detail of the disclosure provided by the Applicant, in view of the prior Art, must encompass a wide area of knowledge to enable one of ordinary skill in the art at the time of the invention to practice the invention without undue experimentation. However, as it will be discussed below this undue experimentation has not been overcame by the as-filed

application. Though, the specification teaches that a phosphtidylinoistol 3-kinase inhibitor can inhibit production of IL-2 induced by CD28 ligation and thus induces unresponsiviness to an antigen, the broad aspects of administering the T cells to a subject with the contemplated used of treating an autoimmune disease is not reasonably enable for the full scope embraced by the claims.

In relation of administration of T cells to treat autoimmune disorders, post-filing art teaches that the cause of autoimmune disorders is generally considered to be T cell mediated, but that the events involved in the treatment of autoimmune diseases may be more complicated. This complex pathogenesis is reflected in the variable response of autoimmune disorders to immunosuppressants. For example, Rott et al., (Clinical Review, 2005, 716-720) teach that patients with rheumatoid arthritis were treated with concomitant immunosuppressant while patients with Crohn's disease don't follow the same regimen of concomitant immunosuppressant (p. 717, col. 2, last paragraph). These different treatments result in distinct immune responses, including immune responses to therapeutic antibodies, development or unmasking of autoimmune disorders and even drug induced lupus after administration of drugs for treatment of autoimmune diseases (e.g., TNF-α inhibitors) (p. 718, col. 2). In addition to the treatment with drugs inhibiting TNF-α, administration of hematopoietic stem cells, (e.g. giving rise to B and T lymphocytes, monocytes, macrophages, and dendritic cells) have been used for treatment of autoimmune disease. Despite a moderate success in the treatment of some autoimmune diseases in animal models by transfer of hematopoietic cells, including type 1 diabetes, systemic lupus erythematosus and autoimmune encephalomyelitis, Sykes et al., (Nature 2005, pp. 620-627) disclose the unpredictability of using hematopoietic-cell transplantation therapy for treatment of

autoimmune diseases in humans when he teaches, " although the prevention of autoimmunity might some day be clinical feasible, at the moment we cannot predict such a diseases accurately enough to justify the use of toxic preventive treatment. Unfortunately, animal studies show that preventing the onset of autoimmunity is much easier than reversing established disease" (p. 620, col. 2, paragraph 3) and "to extend observations from these animal models to humans, several factors must be borne in mind: impact of the complex and varied genetics of humans; the effect of different reagents used and different responses to treatment modalities; the impact of concurrent and complicating co-morbidities in the patients; and the ability ot regenerate an immune sytem after lymphoablative therapy" (p. 621, col. 1 last paragraph bridging to col. 2, paragraph 1). The foregoing observations are especially relevant to the method of inducing unresponsiveness to an antigen in a T cell population and further administering the T cell population to a subject suffering from an autoimmune disease for treatment as envisioned in the instant application, because even assuming the induction of tolerance in autoimmune diseases to an autoantigen at the site of the administration, mobilization of T cells, conditioning regimen, toxicity, outcome, source of T cells, and post administration follow-up need to be disease specific. As the result, the issue of claiming broadly a genus of methods for treatment of autoimmune diseases in a subject comprising administration of a T cell wherein unresponsiveness to an antigen has been induced and thus inhibition of production of D-3 phosphoinositides, has not been addressed by the as-filed specification. Hence, given the unpredictability of the art and the lack of working example in the instant specification, particularly when taken with the lack of guidance in the specification, it would have required

undue experimentation to practice the instant method to identify an enormous number of treatments of autoimmune diseases in a mammal as broadly or generically claimed.

Rejection, Obviousness Type Double Patenting-

The nonstatutory double patenting rejection is based on a judicially created doctrine grounded in public policy (a policy reflected in the statute) so as to prevent the unjustified or improper timewise extension of the "right to exclude" granted by a patent and to prevent possible harassment by multiple assignees. A nonstatutory obviousness-type double patenting rejection is appropriate where the conflicting claims are not identical, but at least one examined application claim is not patentably distinct from the reference claim(s) because the examined application claim is either anticipated by, or would have been obvious over, the reference claim(s). See, e.g., *In re Berg*, 140 F.3d 1428, 46 USPQ2d 1226 (Fed. Cir. 1998); *In re Goodman*, 11 F.3d 1046, 29 USPQ2d 2010 (Fed. Cir. 1993); *In re Longi*, 759 F.2d 887, 225 USPQ 645 (Fed. Cir. 1985); *In re Van Ornum*, 686 F.2d 937, 214 USPQ 761 (CCPA 1982); *In re Vogel*, 422 F.2d 438, 164 USPQ 619 (CCPA 1970); and *In re Thorington*, 418 F.2d 528, 163 USPQ 644 (CCPA 1969).

A timely filed terminal disclaimer in compliance with 37 CFR 1.321(c) or 1.321(d) may be used to overcome an actual or provisional rejection based on a nonstatutory double patenting ground provided the conflicting application or patent either is shown to be commonly owned with this application, or claims an invention made as a result of activities undertaken within the scope of a joint research agreement.

Effective January 1, 1994, a registered attorney or agent of record may sign a terminal disclaimer. A terminal disclaimer signed by the assignee must fully comply with 37 CFR 3.73(b).

Claims 1-6, 7, 8-9 are rejected on the ground of nonstatutory obviousness-type double patenting as being unpatentable over claims 1-4, 7-10 of U.S. Patent No. 6, 632, 789.

Claims 1-6, 7, 8-9 of the instant application are drawn to a method of inhibiting the response by a T cell expressing a CD28 surface receptor which binds a costimulatory molecule comprising contacting the T cell with an agent which acts intracellularly to inhibit production of D-3 phosphoinositides. Claims 2 and 3 further limit the agent to inhibitors of phosphatidylinositol 3-kinase such as wortmannin, quercetin and LY294002 and derivatives or analogs thereof.

Claims 1-4, 7-10 of U.S. Patent No. 6, 632, 789 are drawn to a method of inhibiting the response by a T cell expressing a CD28 surface receptor which binds a costimulatory molecule comprising contacting the T cell with inhibitors of phosphatidylinositol 3-kinase such as quercetin and LY294002 and derivatives or analogs thereof.

Because claims 1-6, 7, 8-9 of the instant application are broadly drawn to an agent which inhibits production of D-3 phosphoinositides, claims 1-6, 7, and 8-9 embrace claims 1-4, 7-10 of U.S. Patent No. 6, 632, 789, which claim quercetin and LY294002 as the specific inhibitory agents of phosphatidylinositol 3-kinase. Thus claims 1-4, 7-10 of U.S. Patent No. 6, 632, 789, are species of the claimed genus in the instant invention and anticipate the claimed genus of agents that inhibits production of D-3 phosphoinositides.

Conclusion

Claims 1-6, 7-9, 15-17, 19-20 and 22 are not allowed.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Maria Leavitt whose telephone number is 571-272-1085. The examiner can normally be reached on M-F.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Joseph Woitach, Ph.D can be reached on (571) 272-0739. The fax phone number for the organization where this application or proceeding is assigned is 703-872-9306.

To aid in correlating any papers for this application, all further correspondence regarding his application should be directed to Group Art Unit 1636; Central Fax No. (571) 273-8300. Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to (571) 272-0547.

Patent applicants with problems or questions regarding electronic images that can be viewed in the Patent Application Information Retrieval system (PAIR) can now contact the USPTO's Patent Electronic Business Center (Patent EBC) for assistance. Representatives are

available to answer your questions daily from 6 am to midnight (EST). The toll free number is (866) 217-9197. When calling please have your application serial or patent number, the type of document you are having an image problem with, the number of pages and the specific nature of the problem. The Patent Electronic Business Center will notify applicants of the resolution of the problem within 5-7 business days. Applicants can also check PAIR to confirm that the problem has been corrected. The USPTO's Patent Electronic Business Center is a complete service center supporting all patent business on the Internet. The USPTO's PAIR system provides Internet-based access to patent application status and history information. It also enables applicants to view the scanned images of their own application file folder(s) as well as general patent information available to the public.

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